REMARKS/ARGUMENTS

Reconsideration of the present application, as amended, is respectfully requested.

The September 23, 2004 Office Action and the Examiner's comments have been carefully considered. In response, claims are amended and added, and remarks are set forth below in a sincere effort to point out patentable features of the claimed invention and to place the application in condition for allowance. The amendments are supported by the application as originally filed. Therefore, no new matter is added.

Inasmuch as the present amendment raises no new issues for consideration, and, in any event, places the present application in condition for allowance or in better condition for consideration on appeal, its entry under the provisions 37 CFR 1.116 is respectfully requested.

INTERVIEW

The courtesy of Examiner Lee in conducting an interview in connection with this application is acknowledged and appreciated. The interview took place on December 10, 2004. Present at the

interview were Examiner Lee and Applicants' attorney, Robert Michal.

During the interview, Applicants' attorney explained the present claimed invention to the Examiner in detail and contrasted the claimed invention to that disclosed and taught in the references of record. As a result of the interview, no agreement was reached regarding the allowability of the claims.

PRIOR ART REJECTIONS

In the Office Action, claims 16-19 are rejected under 35 USC 103(a) as being unpatentable over USP 5,866,911 (Baer) in view of USP 6,272,376 (Marcu et al.) and USP 6,522,345 (Alexander).

In response, claims 16-19 are amended and new claim 20 is added.

The present claimed invention as defined by amended claim 16, which corresponds to the embodiment shown in Fig. 5 of the present application, is directed to a laser scanning microscope including a pulse laser unit (21) configured to oscillate a pulse laser beam to excite a sample (23), a scanning mirror (22) configured to scan the pulse laser beam, a photodetector (25) configured to detect light from the sample and output an analog detection signal, a sampling control circuit (33) which receives

a pulse oscillation signal from the pulse laser unit and generates a trigger signal delayed by a predetermined time, a pulse generator (45) which receives the trigger signal and generates sampling pulse signals for each trigger signal for a predetermined output period in which a fluorescent signal is generated, an A/D converter (27) which converts the analog detection signal from the photodetector to digital data in synchronism with each of the sampling pulse signals, and a memory (29) which stores the digital data from the A/D converter.

Referring to FIG. 5 and FIGS. 6A-6F of the present application, an embodiment of the present invention will be described.

In the embodiment shown in FIGS. 5 and 6A-6F, a pulse signal output from a pulse generator 45 is used as the sampling clock signal for the A/D converter 27. The pulse generator 45 generates a pulse signal as shown in FIG. 6E in synchronism with the trigger signal 38 output from the delay circuit 37. The frequency fp of the pulse signal and the output period ($\Delta t2$) of each pulse of the pulse signal are arbitrarily set using the external input circuit 39. More specifically, the A/D converter 27 executes sampling, using, as a sampling clock signal, a trigger signal from the delay circuit 37, and executes sampling

only within each output period (Δt2) (see FIG. 6E). Accordingly, the fluorescent signal, which attenuates with time, can be reliably sampled, without missing its peaks, by adjusting the delay time (Δt1) of the delay circuit 37 and the output period (Δt2) of each pulse of the pulse generator 45. Moreover, timing adjustment can be executed so that no sampling is executed where no fluorescent signal is generated. For example, when applying the above-described structure to a laser scanning microscope that uses a two-photon process, if sampling is executed one hundred times during the generation of one pulse of a laser beam, the above structure can be used by setting the output period (Δt2) at 10 ns or less and setting the frequency of the pulse signal of the pulse generator 45 at about 10 Ghz, since, in the two-photon process, a laser beam has a pulse frequency of 80 MHz and a pulse width of 100 fs. As is evident from the above, a brighter image can be obtained by reliably sampling the fluorescent signal than in the case of executing sampling which is not synchronized with laser oscillation. Also, there may be a case where the frequency of emission of fluorescence is low, and hence the fluorescent signal is not always generated each time a laser pulse is generated. Even in this case, the fluorescent signal can be acquired efficiently by sampling it in synchronism with

laser oscillation. Furthermore, since the fluorescent signal is reliably sampled without missing its peak(s), and is stored in the memory 29, digital processing using the digital data, such as digital integration of the fluorescent signal, analysis of the maximum value of the fluorescent signal, analysis of the time constant of the fluorescent signal, etc., can be executed. In addition, since the sampling is not executed when a fluorescent signal is not generated, only necessary sampled data need be stored in the memory 29, thereby reducing the memory requirements. Therefore, the remaining memory capacity can be effectively used.

Baer teaches a scan optical system such as a confocal laser microscope wherein a beam of light is focused to a spot in a specimen to excite a flourescent species or other excitable species located at the spot. The effective size of the excitation is made smaller than the size of the spot by providing a beam of light having a wavelength adapted to quench the excitation of the excitable species.

The microscope defined by amended claim 16 has the following advantages. By delaying the start of sampling by a predetermined time period, the peak of fluorescence is detected (the start of sampling is adjusted to coincide with fluorescence) and by

generating two or more sampling pulses for each pulse of the pulse laser and detecting the intensity of fluorescence using each sampling pulse, changes in the intensity of fluorescence over time can be detected. Baer does not disclose, teach or suggest the foregoing advantages of the present claimed invention.

In the Office Action, the Examiner states that Baer teaches providing additional equipment for fluorescence lifetime management. The Examiner contends that equipment for fluorescence lifetime measurements such as conventional commercially available digital oscilloscopes are well known in the art. The Examiner points to USP 6,272,376 (Marcu et al.) and USP 6,522,345 (Alexander) to support his position. The Examiner states that it would have been obvious to one of ordinary skill in the art at the time the invention was made to provide additional equipment such as a conventional commercially available digital oscilloscope in the microscope of Baer in order to obtain fluorescence lifetime measurements.

The present invention is not a mere combination of a laser scanning microscope with a commercially available digital oscilloscope as suggested by the Examiner.

The pulse generator of the present claimed invention generates sampling pulse signals for each trigger signal for a predetermined output period in which a fluorescent signal is generated. The A/D converter of the present claimed invention converts the analog detection signal from the photodetector to digital data in synchronism with each of the sampling pulse signals (see claim 16, lines 11-17). Accordingly, only the actually significant detection signal, within a predetermined period of time after the trigger signal, is converted into digital data. The obtained digital data can be used for analysis of a subsequent stage without further processing.

If Marcu et al. and Alexander et al. are combined with Baer so as to convert the detection signal from the photodetector with a commercially available digital oscilloscope as suggested by the Examiner, <u>the A/D converter and the pulse generator provided in the digital oscilloscope would convert the detection signal at any time (sequentially)</u>. The digital oscilloscope would not convert the detection signal within a predetermined period of time after the trigger signal is converted to digital data. Thus, the process of extracting the actually significant data (i.e. data of the trigger signal for a predetermined output period) from the obtained digital data would have to be

performed. This processing should also be performed inside the digital oscilloscope. For this reason, the digital oscilloscope would have the structure of managing and extracting the desired data corresponding to the sequential digital data stored in the memory. The present invention does not require such structure.

In a digital oscilloscope as taught in Marcu et al. and Alexander et al., sampling pulses are generated at any time. In the present invention, however, sampling pulses are generated during a predetermined output period in which a fluorescent signal is generated (that is, a period required for data acquisition only) (see claim 16, lines 11-17).

As shown in the attached Fig. 2, the present claimed invention samples fluorescence, which is generated by one laser pulse, by a plurality of gates to obtain a fluorescence decay curve with one excitation.

As described at column 7, line 38, USP 6,272,376 (Marcu et al.) discloses that the width of the time gate for fluorescence measurement is 5 nsec (see also Fig. 1 attached hereto). Therefore, to obtain a fluorescence decay curve such as that shown in Fig. 5A of Marcu et al. (attached hereto), it is necessary to obtain a signal by one gate in one excitation, and then to obtain a signal by shifting the position of the gate by

ΔT in another excitation. For example, in Fig. 5A of Marcu et al., it is necessary that ΔT is 0.4 nsec or less to obtain data. Thus, it is impossible to obtain a fluorescence decay curve in one excitation by combining Baer, Alexander and Marcu et al. as compared with the present claimed invention.

If Baer, which is a laser scanning microscope, is combined with Marcu et al., an image must be scanned N times to obtain data of one image, in contrast to the present claimed invention which samples fluorescence, which is generated by one laser pulse, by a plurality of gates to obtain a fluorescence decay curve with one excitation.

That is, the present claimed invention as defined by claim 16 is patentable over Baer, Marcu et al. and Alexander et al. because the references do not disclose, teach or suggest, when taken either alone or in combination, <u>inter alia</u>, a laser scanning microscope including:

1. a sampling control circuit which receives a pulse oscillation signal from the pulse laser unit and generates a trigger signal delayed by a predetermined time; and/or

2. a pulse generator which receives the trigger signal and generates sampling pulse signals for each trigger signal for a

predetermined output period in which a fluorescent signal is generated; and/or

3. an A/D converter which converts the analog detection signal provided by the photodetector to a digital signal in synchronism with each of the sampling pulse signals (see claim 16 lines 8-16).

In view of the foregoing, claim 16 and claims 17-19 which are dependent thereon and further define and limit the invention defined by claim 16 are patentable over the cited references under 35 USC 102 as well as 35 USC 103.

NEW CLAIM

New claim 20 is added to the present application. New claim 20 is dependent on claim 16 and further defines the invention recited in claim 16. Claim 20 is patentable over the cited references in view of its dependence on claim 16, and because the references do not disclose, teach or suggest each of the limitations set forth in claim 20.

It is respectfully believed that no additional fees are due for the presentation of claim 20. If, however, any fees are due, please charge our Deposit Account No. 06-1378 for such sum.

Entry of this Amendment under the provisions of 37 C.F.R. 1.116, allowance of the claims and the passing of this application to issue are respectfully solicited.

If the Examiner disagrees with any of the foregoing, the Examiner is respectfully requested to point out where there is support for a contrary view.

If the Examiner has any comments, questions, objections or recommendations, the Examiner is invited to telephone the undersigned at the telephone number given below for prompt action.

Respectfully submitted,

Robert P. Michal
Reg. No. 35,614

Frishauf, Holtz, Goodman & Chick, P.C.
767 Third Avenue - 25th Floor
New York, New York 10017-2032
Tel. (212) 319-4900
Fax (212) 319-5101
RPM/ms

Encl.: Petition For Extension of Time